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Oct. 4, 2010 — Joanne Bourguignon

Date — Joanne Bourguignon

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Appellants	:	Rodney J. Ho et al.
Application No.	:	10/757,775
Filed	:	January 14, 2004
For	:	LIPID-DRUG FORMULATIONS AND METHODS FOR TARGETED DELIVERY OF LIPID-DRUG COMPLEXES TO LYMPHOID TISSUES
Examiner	:	Umamaheswari Ramachandran
Art Unit	:	1627
Docket No.	:	42474.03US2
Date	:	October 4, 2010

REPLY BRIEF UNDER 37 CFR 41.41(a)(1)

Mail Stop Board of Patent Appeals and interferences
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer dated August 2, 2010, Applicants reply as follows:

This response is intended to reply to the Response-To-Argument section in the Examiner's Answer that begins on page 9 of the Examiner's Answer. Appellants continue to rely on the arguments presented in the originally filed Appeal Brief with respect to the current claim rejections. On the second-to-last line of page 10, the Examiner states:

> The dissociation of the drug from the complex at the claimed pH range is the property of the lipid-drug complex," is not conclusory as Applicants argue because, Kirpotin's lipid-drug complexes comprise the same lipids and drugs

> as claimed by the Applicants as shown above and accordingly, the dissociation property of the lipid-drug complexes of Kirpotin would be expected to be substantially similar as claimed by the Applicants, including that "at least one drug molecule substantially disassociates from the lipid-drug complex within a pH range of about 5.0-5.5". The low aqueous solubility is a property of the drug and the dissociation of the drug at a certain pH is the property of the drug and the drug complex.

The Examiner's response appears to completely fail to consider arguments provided in the Appeal Brief. As discussed in the Appeal Brief, the currently claimed lipid-drug complex is prepared by a different method than Kirpotin's disclosed drug-encapsulating liposomes. Those familiar with chemistry, biochemistry, and molecular biology well understand that the structure and contents of a complex molecular aggregate containing thousands, hundreds of thousands, or millions of molecules may, in fact, be determined by the procedure used to prepare the molecular aggregate. As pointed out in the Appeal Brief, a lipid can, under differing conditions, form bilayer spheroids, micelles, unilamellar structures, and quite possibly many hundreds or thousands of specific, distinct types of aggregates that differ from one another in structure, composition, and chemical and physical characteristics. There is simply no basis for the Examiner to conclude that Kirpotin's drug-encapsulating liposome, prepared by a method different from preparation of the currently claimed lipid-drug complex, is identical to, or has similar characteristics as, the currently claimed lipid-drug complex. It is extremely well known than many different types of molecular aggregates can be produced from lipids. The chance that complex molecular aggregates prepared by different methods would be identical is vanishingly small. There is, in particular, no reason to conclude that the currently claimed characteristic, "wherein the at least one drug molecule substantially dissociates from the lipid-drug complex within a pH range from about pH 5.0 to about pH 5.5," is commonly shared by the currently-claimed lipid-drug complex and the Kirpotin's drug-encapsulating liposome, and the Examiner has provided no reason or rationale for the Examiner's conclusory assertions, other than to repeat the assertions.

The Examiner continues to try to shift the burden of examination to Applicants, stating that the "Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product." Kirpotin does not state, claim, or suggest that his drug-encapsulating liposomes allow the drug to disassociate from the complex in the pH range at which the currently claimed lipid-

drug complex allows for dissociation of the drug from the lipid complex. Kirpotin's drug-encapsulating liposomes are prepared by a different method than the currently claimed lipid-drug complex. Kirpotin indicates that, in the currently claimed pH range of about pH 5.0 to about pH 5.5, the drug within the drug-encapsulating liposomes prepared by Kirpotin is precipitated. A precipitated drug is not soluble, but is instead in solid form. If Kirpotin's drug-encapsulating liposomes remains intact, Appellants' representative knows of no biological, biochemical, or chemical principle by which the precipitated, insoluble drug would end up dissociating from the drug-encapsulating liposomes of Kirpotin. The interior of a liposome is isolated by the lipid membrane from exterior of the liposome. The liposome membrane is generally impermeable to water, aqueous solutions, and to solids. Because there is no evidence provided by the Examiner, other than a conclusory statement, to suggest that the currently claimed lipid-drug complex is identical to Kirpotin's liposome, as discussed in the previously filed Appeal Brief, the Examiner cannot shift the burden of examination onto Applicants. The Examiner must provide some reasonable and rational reason to support the assertion that Kirpotin's drug-encapsulating liposome is identical to, and has the same characteristics as, the currently claimed drug-lipid complex, despite being prepared by a different method, and despite the fact that Kirpotin states that the drug is precipitated within the drug-encapsulated liposome in the pH range that the currently-claimed lipid-drug complex releases the drug.

On page 12-13 of the Examiner Answer, the Examiner states:

> In response to Applicants' argument that Kirpotin's method of preparing lipid-drug complexes is very different than the currently claimed lipid-drug complex, the claims of the instant invention are towards a composition comprising at least one lipid molecule, at least one drug molecule having low aqueous solubility and the method of preparation is irrelevant here because given the broadest reasonable interpretation of the claim and not importing the claim limitations from the specification to the claim, the claims of the instant invention are towards a composition comprising at least one lipid molecule, at least one drug molecule having low aqueous solubility and the claims are not towards a process or method of making comprising different steps. There are no limitations in the claims that the composition is prepared in a specific technique or consists of specific components with any specific amounts. The claims are towards a composition with a comprising language and are very broad with respect to the active ingredients in the claims including the lipids, the drugs and their amounts.

The Examiner appears to have failed to appreciate Appellants' arguments provided in the originally filed Appeal Brief. Current claim 1 is directed to a lipid-drug complex comprising

at least one lipid molecule and at least one drug molecule having low aqueous solubility within a neutral pH range and "wherein the at least one drug molecule substantially dissociates from the lipid-drug complex within a pH 5.0-5.5 range." The claimed dissociation of the drug molecule from the lipid-drug complex is a claim limitation. It is as much a claim limitation as the drug molecule and lipid molecules. There is no reason for the Examiner to assert or suspect that "the dissociation properties of Kirpotin's lipid-drug complexes would be expected to be substantially similar to the properties of the claimed composition," as the Examiner asserts on page 13, following the above-quoted passage. Kirpotin does not in any way indicate that the drug dissociates Kirpotin's drug-encapsulating liposomes at this pH range, and Kirpotin indicates this pH range corresponds to the minimum solubility of the drug. If the drug is precipitated within Kirpotin's liposome at this pH range, then it is difficult to imagine how a precipitated, insoluble, solid drug could dissociate from Kirpotin's drug-encapsulating liposome unless the integrity of the liposome is somehow compromised. Those familiar with biochemistry and chemistry understand that, in general, neither solids nor solution are exchanged between the interior of a liposome and the exterior of a liposome. Indeed, all living cells take advantage of this fact to generate and maintain a variety of different chemical gradients and electrical potentials across cell membranes, which are essentially lipid bilayers. By contrast, Appellants have provided very good reasons why Kirpotin's drug-encapsulating liposomes are most likely different from the lipid-drug complexes to which the current claims are directed.

On pages 13-14 of the current application, the Examiner states:

> The reference in col. 8, lines 34-37 teaches that the internal pH of the liposomes in the composition is preferably at or near the minimum solubility pH of the precipitated compounds, or at a lower pH of 4 to 5.5 or an upper pH of 8.5-10. Accordingly, the drug or the compound can be precipitated at 3 different pH conditions. Hence a compound such as indinavir with the low aqueous solubility of appreciably soluble only at very low pH can be precipitated at or near the minimum solubility pH of indinavir or at an upper pH of 8.5-10. If precipitated at those pH conditions the drug can dissociate at a pH range of 5.0-5.5.

Appellants' representative has no idea what the Examiner is attempting to state in this passage. There is no reason to suspect that a precipitated drug can dissociate from the interior of a drug-encapsulating liposome. Appellants' representative knows of no reasonable or rational chemical or biochemical explanation or proposal other than a disruption of the liposome that would allow the interior contents of the liposome to escape encapsulation.

Kirpotin does not teach, mention, disclose, or even remotely suggest degradation of his drug-encapsulating liposome at this pH range. The Examiner's statement is conclusory and is not scientifically reasonable or rational. A precipitated drug does not traverse a liposome membrane. Furthermore, Appellants' representative has no idea to what 3 pH conditions the Examiner is referring to. The passage on lines 34-37 of column 8 of Kirpotin states that the drug is precipitated within drug-encapsulating liposome. The statement appears to suggest that the minimal solubility for the drug occurs in a range of pH 5.5 to 8.5, but does not suggest that the drug is soluble in the ranges pH 4 to 5.5 or pH 8.5 to 10. Instead, the passage suggests that the drug is precipitated within the drug-encapsulating liposome over the range pH4 to pH 10. That being the case, the only reasonable conclusion that can be made is that the drug cannot dissociate from the drug-encapsulating liposome in the pH range of 4.5 to 10.

In summary, as previously stated in the Appeal Brief, Appellants believe that the currently claimed lipid-drug complex is different from, and has different characteristics than, Kirpotin's drug-encapsulating liposome. Kirpotin's drug-encapsulating liposome is prepared by a different method than the currently claimed lipid-drug complex. Those familiar with biochemistry and chemistry realize that, when a complex aggregate of many thousands to millions of molecules is prepared by different procedures, it is very likely the products of the different preparation methods are themselves different. In fact, the probability that two such complex aggregates would be identically produced by different methods is infinitesimally small. As pointed out in the Appeal Brief, depending on the method of preparation, complexes of lipids can form many different types of molecular aggregates. Although the Examiner continues to make conclusory statements to the effect that Kirpotin's drug-encapsulating liposome allows dissociation of the encapsulated drug at the pH range 5.0-5.5, Kirpotin does not state this and, to the contrary, states that the drug is precipitated within Kirpotin's drug-encapsulating liposome in this pH range. As those familiar with biochemistry and chemistry well realize, there is no reasonable chemical or biochemical phenomenon or pathway for precipitated solids to leave the interior of a liposome and end up in the solution external to the liposome. The Examiner's assertions and statements to the contrary are purely conclusory and are not scientifically reasonable or rational.

Applicants respectfully submit that all statutory requirements are met and that the present application is allowable over all the references of record. Therefore, Applicants respectfully request that the present application be passed to issue.

Respectfully submitted,
Rodney J. Ho et al.
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